UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/190,043 | 11/10/98 | HOUCK J | 47.653.2 |

EXAMINER

HM12/0309

GEORGE W NEUNER
DIKE BRONSTEIN ROBERT & CUSHMAN
130 WATER STREET
BOSTON MA 02109

BORIN, M

| ART UNIT | PAPER NUMBER |
|---|---|
| 1631 | 11 |

DATE MAILED: 03/09/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/190,043 | Houck et al. |
| **Examiner** | **Group Art Unit** |
| M. Borin | 1631 |

☒ Responsive to communication(s) filed on *Dec 30, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) *4-20* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Status of Claims*

1. Amendment filed 12/30/99 is acknowledged. Amendments to specification has been entered, except for amendment to p. 19: there is no such peptide sequence on this page as identified in the amendment. Claims 1-20 are pending. Claims 4-20 are withdrawn from consideration. Cancellation of claims 4-20 is requested.

### *Sequence Listing*

2. The Sequence Listing was approved by STIC for matters of form.

### *Claim Rejections - 35 U.S.C. § 103.*

3. Applicants arguments with respect to rejection made under 35 U.S.C. 103 have been considered but are not deemed to be convincing for the reasons stated below. For clarity, the outstanding rejections in this case are stated below. The text of those sections of Title 35, U.S. Code not included in this Office action can be found in a prior Office action.

4. Claims 1-2 are rejected under 35 U.S.C. 103(a) as obvious over Gleisner (Inflammation, 5, 13-17, 1981) in view of Oxford Dictionary of Biochemistry and Molecular Biology (1981) and Casale and Dimitrascu, and further in view of Kermode, Ferry and Anderson.

The instant claims are drawn to method for treating allergy reaction by formyl Met peptides having formula f-Met-Leu-X.

Gleisner teaches that formyl Met peptides are capable of reducing effect of other pro-inflammatory agents (such as 48/80, anti-rat IgE, etc) in that they inhibit the evoked mast cell degranulation and histamine release. Particular examples of the formyl Met peptides are f-Met-Phe, f-Met-Leu-Phe. The study concludes that the formyl Met peptides described in the reference as well as their structural analogs can be a useful addition to the existing antihistaminic drugs. See p. 16, end. It is well known that antihistamine drugs are used in the treatment of allergy reactions. See, e.g., Oxford Dictionary of Biochemistry and Molecular Biology, 1997, p. 43. It is well known as well that mast cells are the most important cells in the development of allergenic response. References of Dumitrascu and Casale are provided as an example. Therefore, it would be obvious to use formyl Met peptides in the treatment of allergy reactions.

In regard to particular formyl Met peptides, a variety of preferred species of formyl Met peptides is known in the prior art. Thus Kermode (reference AE) discloses that formyl Met peptides, such as f-Met-Leu-Phe, f-Met-Leu-Phe-Phe and f-Nle-Leu-Phe-Tyr as functional equivalents. In particular, f-Met-Leu-Phe-Phe is one of the most potent formyl Met peptides analogs. See p.276, first paragraph; Tables 1,2; Fig.2;p. 719. Similarly to Kermode reference, Ferry et al. (Reference AM) teach formyl Met peptide, f-Met-Leu-Tyr.

The cited reference discussing formyl Met peptides do not disclose peptides f-Met-Leu-Phe-Tyr and f-Met-Leu-Tyr-Phe. Anderson (reference AC) teaches that the requirements for the core

structure of biologically active formyl Met peptide analogs are the following: N-acyl formyl group, a Met or Nle residue in position 1, Leu, Val or Ile residue in position 2, and an aromatic amino acid in position 3; a formyl Met peptide analog can be either a tripeptide or a tetrapeptide. See p. 253, Discussion section, first paragraph. As an example, Anderson teaches such formyl Met peptides as f-Met-Leu-Phe, f-Met-Leu-Tyr. See Table 2. In regard to the instantly claimed peptide f-Met-Leu-Phe-Tyr, it would have been *prima facie* obvious to one of ordinary skills in art at the time the invention was made to be motivated to substitute Nle for Met residue in position 1 of the peptide f-Nle-Leu-Phe-Tyr reported by Kermode, because Anderson teaches that biological activity of the peptides is retained when the residue in position 1 is either Nle or Met. One would expect that formyl Met peptide analog obtained by such substitution would have the same biological properties, i.e., activate functions of neutrophils. In regard to the instantly claimed peptide f-Met-Leu-Tyr-Phe, it would have been *prima facie* obvious to one of ordinary skills in art at the time the invention was made to be motivated to substitute Phe for Tyr residue in position 3 of the peptide f-Nle-Leu-Phe-Phe reported by Kermode, because Anderson teaches that the residue in position 3 can be an aromatic amino acid, such as Phe or Tyr (see examples in Anderson, Table 2, lines 1, 2). One would expect that formyl Met peptide analog obtained by such substitution would have the same biological properties, i.e., activate functions of neutrophils.

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are fully envisioned by the teaching of the references cited above.

Response to arguments

On the onset, Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 U.S.C. 103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. It has been well established that the test for combining references is not what individual references themselves suggest but what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin,* 170 USPQ 209 (CCPA 1970).

In discussing Gleisner reference, applicant argues that the reference does not teach or suggest inhibition of degranulation by f-Met peptides. Examiner agrees with the lack of teaching of such effect. However, the claims are not drawn to the effects of degranulation, but are rather drawn to treating an allergy reaction. The latter, not the former effect, is addressed in the rejection. It would have been obvious to use formyl Met peptides in the treatment of allergy reactions because they act as antihistamines by preventing histamine release caused by other pro-inflammatory agents.

Applicant further points to the fact that Kermode teaches away from the claimed method because it shows that f-Met peptides stimulate, rather than prevent degranulation. First, it is not surprising that Gleisner (the primary reference) and Kermode (a secondary reference) teach opposite effects of f-Met peptides: In Gleisner, f-Met peptides are used after degranulation has been stimulated by other pro-inflammatory agent. In contrast, in Kermode f-Met peptides cause degranulation when used alone, without a previous exposure of cells to pro-inflammatory agent. Second, Kermode reference are used in the rejection merely to demonstrate that formyl Met peptides, such as f-Met-

Leu-Phe, f-Met-Leu-Phe-Phe and f-Nle-Leu-Phe-Tyr as functional equivalents. Same applies to other secondary references used in the rejection.

5. Claim 3 is rejected under 35 U.S.C.103(a) for the reasons set forth in the rejections of claims 1,2 above and further in view of Goodman and Gilman (p. 170; reference AL).

The instant claims are drawn to combination therapy including formyl Met peptides discussed above and other active ingredients, such as anti-leukotriens, beta agonists, etc.

Use of other ingredients claimed in the instant claim for treatment of allergy is very well known in the art. See, e.g., Goodman and Gilman , p. 170(reference provided by the applicant). It is well known that it is prima facie obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. In re Pinten, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); In re Susi, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). As the court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

Response to arguments

The rejection of claim 3 is maintained as for the reasons of record and in view of the confirmed validity of claims 1-2 (as discussed above).

***New ground of rejections: 35 U.S.C. § 112, first paragraph.***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating an allergy reaction caused by other pro-inflammatory agents which induce of mast cells degranulation, does not reasonably provide enablement for pharmaceutical use of f-met peptides in the absence of exposure to such pro-inflammatory agents.

The invention is drawn to treatment of allergy reaction using formyl Met peptides. The breadth of the claims is not limited to any particular dosage range or specific circumstances of generation of allergy reaction. It is well known in the prior art that f-Met peptides are known mostly for their inflammatory effect. See, e.g., applicant's arguments on pages 3 (bottom), 6 of the response which clearly present this point. Further, Ferry et al, as described in the art rejection above, teaches that the use of f-Met peptides in high dosage results in an induced disorder (colitis). Thus, the prior art teaches that the effect of f-Met peptides can be opposite to claimed treatment of allergy response and can be harmful altogether. Except for the case when f-Met peptides are applied after another degranulating agent, there is no proper guidance in the prior art in regard to dosage ranges and conditions under which the f-Met peptides, *per se*, would be useful in treating allergy reactions. The instant specification also fails to provide a sufficient guidance in this regard. The range 0.1 to

100,000 μg/kg a day, indicated on p. 13, encompasses 6 orders magnitude in the dosage, i.e. a range which will most likely encompass both inoperative and harmful effects. The experimental data presented in Figures 1-3 are presented in different concentration units (nMoles) and are not comparable with the above general dosage range. The working examples are limited to the demonstration of inhibition of induced mast cell degranulation caused by other inducers of degranulation.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

***Conclusion.***

7. No claims are allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Mr. Michael

Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

9. The Art Unit of your application in the PTO has changed. To aid any papers for this application, all further correspondent should be directed to Art Unit 1631.

MICHAEL BORIN, PH.D
PATENT EXAMINER

March 8, 2000

mlb